REMARKS

Reconsideration and withdrawal of all rejections is respectfully requested in view of the above-provided amendments and the following remarks.

STATUS OF THE CLAIMS

Claims 55, 57-58, 61-75, 77-86, 88-90 and 92-109 are pending. Claims 72-73 and 99-109 have been withdrawn from active prosecution by the Examiner as directed to non-elected subject matter. Claims 77, 87 and 91 are newly cancelled. Claims 1-54, 56, 59-60 and 76 were previously cancelled.

AMENDMENTS TO THE SPECIFICATION

In the specification, literal support for the wording of original claims 31 and 32 has been inserted at page 6, after line 4, in order to provide express support in the specification for the subject of original claims 31 and 32, as now found in claims 55, 65 and 88. Literal support for the wording of original claim 33 has been inserted at page 7, after line 18, to provide express support in the specification for the subject of original claim 33, now found in claim 85.

No new matter is added.

AMENDMENTS TO THE CLAIMS

The claims are amended to more particularly set forth that which Applicants consider to be their invention.

Claims 55 and 88 are amended to recite that the interferon-*beta* 1b is conjugated to a polyalkylene oxide conjugate "that ranges from about 30kDa to about 40 kDa..." Support for these amendments is found, for example, in now-canceled dependent claim 91 and in the specification, e.g., at page 14, lines 20-21. Claim 55 is also amended to recite that "at least about 20 percent of the antiviral activity is retained relative to native interferon-*beta* 1b, using the EMC/Vero or EMC/A549 antiviral bioassay." Support for this is found, for example, in now-canceled claim 87 and original claim 32.

All claim amendments simply copy the elements of dependent claims to main claim(s). Thus, it is respectfully urged that no new matter is added to the claims after Final, and entry of all claim amendments is respectfully requested.

No new matter is added.

TELEPHONE INTERVIEW

Applicants express their appreciation for the telephone interview conducted with the Examiner on May 11, 2011, with Applicants' undersigned attorney. While no agreement was reached concerning patentable subject matter, the Examiner provided several helpful suggestions for the instant response.

THE CLAIMS ARE NONOBVIOUS UNDER 35 U.S.C. § 103(a)

The Examiner has maintained the three rejections previously made under 35 USC 103(a).

Rejection 1. On pages 2-5 of the Final Office Action, claims 55, 57-58, 61-71 and 80-95 are again rejected under 35 USC 103(a) as allegedly obvious over Drustrup et al. ("Drustrup;" US Patent Publication No. 2003/0138403) in view of Durelli et al. ("Durelli;" The Lancet, 2002, 359:1453-1460, IDS filed 12/22/2006).

The Examiner repeats his previous position that Drustrup teaches IFN-beta conjugated to a 12kDa PEG formulated with an acetate buffer (10mM) and mannitol (defined by the Examiner as an excipient) at a pH of 5.5 (Drustrup, Example 5.5, ¶0393). The Examiner concedes that Drustrup is silent as to a composition including IFN-beta-1b. The Examiner again cites Durelli as remedying this deficiency by teaching advantages in treating patients with multiple sclerosis ("MS") with IFN-beta-1b, relative to treating MS with IFN-beta-1a. The Examiner concludes that it would have been obvious to create the composition of claim 1, given the teachings of Drustrup, and the above-noted teachings of Durelli. The Examiner has also assumed that the IFN composition of the alleged combination inherently retains IFN activity as required by claims 86 and 87, absent evidence to the contrary.

In addition, at page 4 of the Office Action, the Examiner takes the position that Pepinsky and Runkel, cited by Applicants, do not teach away from the claimed invention, because Durelli teaches that IFN-beta 1b is effective in treating multiple sclerosis.

Applicants respectfully disagree.

The Examiner has cited Drustrup, and concedes that Drustrup is silent as to a composition specifically including IFN-beta-1b. The Examiner cites Durelli to argue that IFN-*beta*-1b would have been known to be more potent/effective than IFN-*beta*-1a *in vivo*, in the treatment of multiple sclerosis. Durelli reports a 2-year, prospective clinical trial identified as "INCOMIN" that compared these two IFN-*beta* analogs. The INCOMIN study administered IFN-beta 1b every other day, and IFN-*beta* 1a once per week. It is submitted that the disparity in dose regime between IFN-*beta* 1b and 1a in the INCOMIN study would not have taught or suggested the invention, taken alone or in any combination with Drustrup, to the artisan, because:

(a) The disparity in dosing regimes (weekly verses every other day) used by the INCOMIN study would have made it impossible to draw any conclusions as to the relative potency of the two IFN analogs when conjugated to a polyalkaline oxide, e.g., PEG.

(b) The artisan, seeking a long-acting conjugate, would still have looked to IFN-*beta* 1a administered once per week and not to IFN-*beta* 1b, based on the reported dosing schemes for the INCOMIN study.

(c) Claims 55 et seq. are limited by the requirement that the conjugated IFN-*beta* 1b that is part of the claimed stable composition, retain at least 20 percent of its **antiviral activity** in that composition. It is submitted that Durelli is completely silent as to the **antiviral** activity of IFN-*beta* 1a/1b, in absolute or relative terms, and that the artisan would not have looked to any combination of Drustrup and/or Durelli as a guide to the composition of claim 55, et seq.

During the above-mentioned telephone interview, the Examiner agreed that he did not provide his evaluation of the following analysis of the reasons that the invention is nonobvious, as presented in the previous Response. The Examiner's attention to this will be appreciated.

At the time that the invention was made, the ordinary artisan would have had Pepinsky and Runkel, teaching the relative advantages of IFN-beta-1a (over IFN-beta 1b) for administration as a polymer conjugate. As stated in the previous Response:

As described in the Pepinsky text bridging pages 1063-1064,

> In selecting the 20-kDa PEG aldehyde adduct, we first screened a variety of sized PEGs for their effects on pharmacokinetics and activity in the antiviral assay. Lower molecular weight PEG aldehyde IFN-b-1a conjugates were fully active, but failed to produce the desired enhancement in pharmacokinetic properties. Higher molecular weight forms, in contrast, which should further improve the pharmacokinetic properties of the molecule, compromised activity. (Underline added for emphasis).

Thus, given the potency data as confirmed by Runkell, and the relative pharmacokinetics of the respective conjugates as reported Pepinsky, it would not have been expected that the less potent IFN beta 1b would have provided good kinetics and retention of potency (ie, antiviral activity) when polymer conjugated, relative to the PEGylated IFN beta 1a of Pepinsky. See, for example, page 6 of the instant patent application, last full paragraph and Example 5H, showing retained antiviral activity (compare to Pepinsky). It is submitted that the different dosing regimes of the Durelli INCOMIN study, and the fact that Durelli, as a source of data on the relative advantages of interferons, is silent as to the benefits of polyalkylene oxide conjugated conjugation, and especially as to retained antiviral activity. This would have prevented the artisan from drawing any conclusions or expectations, as to the relative expectation of success for the higher molecular weight PEGylated IFN-beta-1b, relative to PEGylated IFN-beta-1a. It is submitted that the artisan, considering the possible advantages of polymer conjugated IFN-1a relative to 1b would have looked to the results of Pepinsky, and not to the results of Durelli.

It is further submitted that, given the teachings of Pepinsky and Runkel, the initial burden is on the Patent Office to come forward with persuasive technical reasons why the ordinary artisan, given Pepinsky and Runkel, would have thought to provide a polyalkylene oxide conjugated IFN-beta 1b, in the claimed formulation. It is urged that Durelli is not sufficient for this purpose, given the different dosing schemes employed in that study, the testing on multiple sclerosis, and given the lack of any data, whether *in vivo* or *in vitro*, as to the relative antiviral effectiveness or potency for polymer conjugated interferons.

The Examiner is respectfully reminded that the claims must be considered as a whole. The instantly rejected claims are directed to compositions (claims 55, 57-58, 61-71 and 80-86) and methods of preparing the subject compositions (claims 88-90 and 92-95). The inventive compositions solve a problem of providing a stable composition of the polyalkylene oxide conjugated IFN-beta-1b taught by the invention.

The specification provides a range of test data showing the advantages and disadvantages

of various composition parameters. Claim 61 is directed to the composition of claim 55, but requiring a pH ranging from pH 3.0 through pH 4.0. At page 28 of the specification, in the Table of Example 5A, it is confirmed that compositions at pH 3.0 and pH 4.0 resulted in 0% aggregation of the tested PEG-IFN-beta-1b. This contrasted with clear evidence of aggregation observed at higher pH values. It is submitted that the art of record would not have taught or suggested making the composition of claim 55 and/or 61, given these unexpected results and the unpredictability of the art of compositions and protein formulations.

In addition, independent claim 85 is directed to a liquid composition comprising *inter alia* an acetic acid buffer with a pH of about 3.7. This is respectfully urged to be a specific acid pH range that would not have been suggested by the alleged references.

For all of these reasons, it is respectfully submitted that all of the foregoing rejections under 35 USC 103(a) be reconsidered and withdrawn.

Rejection 2. On page 5 of the Final Office Action, claims 74, 77-79 and 96-98 are rejected under 35 USC 103(a) as allegedly being unpatentable over Drustrup (as above), in view of Durelli (as above), and further in view of McManus et al. ("McManus;" US Patent Publication No. 2007/0166277).

The Examiner concedes that both Drustrup and/or Durelli are silent as to the particular species of PEG required by claim 74, or the terminal reactive moiety of claim 98. The Examiner cites McManus as remedying this deficiency by teaching a succimidyl ester of a 40 Kda branched PEG, that is stated to correspond to the species of claim 74, including the terminal moiety of claim 98, and at paragraph 0172, with the same spacer, including conjugation to IFN-beta-1b (citing to Example 15). The Examiner concludes that it would have been obvious to create the composition of claims 74, 77-79 and 96-98, given the teachings of Drustrup with Durelli and McManus.

Applicants respectfully disagree.

Claims 74, 77-79 and 96-98 ultimately depend from claim 55, and as a matter of law, are nonobvious if claim 55 is nonobvious. The Examiner's attention is respectfully directed to the above provided traversal of the rejections of claim 55, et seq., on the grounds that Drustrup and/or Durelli would have failed to teach or suggest a polyalkylene oxide conjugate of IFN-beta-

1b according to claim 55, and that Drustrup and/or Durelli would have failed to teach or suggest a composition comprising the polyalkylene oxide conjugate of IFN-beta-1b according to claim 55. Certainly, McManus fails to remedy these clear deficiencies, since McManus, at best, teaches a species of polyalkylene oxide, without more.

For all of these reasons, it is respectfully submitted that all of the foregoing rejections under 35 USC 103(a) be reconsidered and withdrawn.

Rejection 3. On pages 8-9 of the Office Action, claim 75 is rejected under 35 USC 103(a) as allegedly unpatentable over Drustrup (as above), in view of in view of Durelli (as above), and further in view of Saifer et al. ("Saifer;" US Patent Publication No. 2004/0126361).

The Examiner takes the position that the particular polypeptide of IFN-beta-1b adds no patentable weight to the main claim. The rejected claim is directed to an IFN-beta-1b of SEQ ID NO: 1. The Examiner concedes that Drustrup with Durelli fails to point to this specific polypeptide, but cites Saifer to remedy this deficiency.

Applicants respectfully disagree.

The Examiner's attention is respectfully directed to the above provided traversal of the rejections of claim 55, et seq., on the grounds that Drustrup and/or Durelli would have failed to teach or suggest a polyalkylene oxide conjugate of IFN-beta-1b according to claim 55, and that Drustrup and/or Durelli would have failed to teach or suggest a composition comprising the polyalkylene oxide conjugate of IFN-beta-1b according to claim 55. Certainly, Saifer fails to remedy these clear deficiencies, since Saifer, at best, teaches a species of IFN-beta-1b, without more.

Claim 75 ultimately depends from claim 55, and as a matter of law, is nonobvious if claim 55 is nonobvious.

For all of these reasons, it is respectfully submitted that all of the foregoing rejections under 35 USC 103(a) be reconsidered and withdrawn.

FEES

No fees are believed to be owed for entry of the instant amendment. However, in the event that it is determined that any fee is required, the Commissioner is authorized to treat this

paper as the required authorization, and to charge or credit any required fee to Deposit Account No. 02-2275.

This Amendment is submitted with a Petition for a One Month Extension of Time, and the required fee. However, in the event that it is determined that any additional extension of time is required, the Commissioner is authorized to treat this paper as the required petition for extension of time, and to charge any required fee to Deposit Account No. 02-2275.

Pursuant to 37 C.F.R. 1.136(a)(3), please treat this and any concurrent or future reply in this application that requires a petition for an extension of time for its timely submission as incorporating a petition for extension of time for the appropriate length of time. The fee associated therewith is to be charged to Deposit Account No. 02-2275.

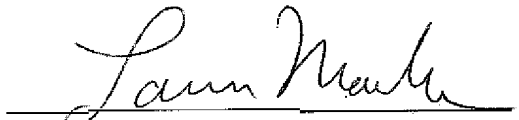
CONCLUSION

In view of the actions taken and arguments presented, it is respectfully submitted that each and every one of the matters raised by the Examiner have been addressed by the present amendment and that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited. Applicants also respectfully request the Examiner to contact the undersigned to resolve any questions or issues that might remain.

Respectfully submitted,

LUCAS & MERCANTI, LLP

By: 

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